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*Joseph Lucas, Fecit*

PANEL IN FOUNDERS AND STAFF ROOM

# THIOURACIL IN THE TREATMENT OF COMPLICATED HYPERTHYROIDISM

## *Report of Six Cases*

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Since the work of the Mackenzies[1, 2] and of Astwood and others[3, 4] the use of thiouracil and related drugs has effected an important advance in the study of thyroid disease and may bring about a permanent change in the principles of their clinical management. Many cases have been reported, but opinions about the usefulness of these drugs vary widely. Enthusiastic observers tend to believe that thyroidectomy for hyperthyroidism will be replaced by medical treatment[5]. Others recommend the preoperative use of thiouracil for more complete control of hyperthyroidism[6]. Still others believe that the drug is dangerous and that compared with the well proved value of iodine and surgery, its disadvantages outweigh its benefits. Whatever the final decision may be, it should be kept in mind for the present that a definite mortality rate, probably somewhat over 0.5 per cent, is directly connected with the use of the drug and is entirely apart from the mortality rate of hyperthyroidism itself. It seems likely that this risk superimposed on the risk of the disease exceeds the mortality rate with treatment with iodine and competent surgery. It is possible that some of the newer related drugs, such as thiobarbital, are less toxic. It has been suggested recently[7] that vitamin $B_6$ (pyridoxine) may be useful in the treatment of leukopenia of toxic origin such as may occur in the course of thiouracil therapy. Many important questions remain to be answered, among which are whether or not treatment with thiouracil will be followed by a continued remission of symptoms after the drug is stopped, how consistently such a remission can be depended upon, and how permanent it will be. The final answer remains in the future.

Even in the hands of the most conservative, however, a trial of thiouracil or related drugs seems clearly indicated in some cases, including those in which response to standard therapy is poor or in which complicating factors are present and surgery is contraindicated. Six such cases, which showed a wide variation in response to thiouracil, were selected for this report.

## CASE REPORTS

**Case 1**—A woman, aged 70, was seen on June 24, 1943 because of goiter and sugar in the urine. Systolic blood pressure was 220 and diastolic 95 mm. of mercury. The pulse rate was 130 per minute. Height was 59 inches and weight 86 pounds. Both lobes of the thyroid gland showed visible nodular enlargement, the right lobe extending below the clavicle. Cardiac dullness extended to the anterior axillary line. Cardiac rhythm was regular, and a systolic murmur was heard at the apex. There was a moderate degree of pitting edema of the ankles. The liver was palpated one finger's breadth below the costal margin. The urine showed 4 plus sugar, and the blood sugar was 428 mg. per 100 cc. two and one-half hours after a meal.

Diagnoses of nodular goiter with hyperthyroidism, cardiac enlargement and decompensation, diabetes mellitus, and varicose veins of the legs were made.

June 27—Admitted to the hospital. B.M.R. plus 48. Diabetic regimen, digitalis, and Lugol's solution, 1 cc. three times a day. Operation contraindicated. X-ray therapy, 1200 r, to thyroid.

July 14—Discharged on Lugol's solution, 5 minims a day, and diabetic care: carbohydrate 338 Gm., protein 114 Gm., and fat 187 Gm., calories 3581. Crystalline insulin four times daily with meals and at bedtime as follows: 46 units, 36 units, 40 units, and 10 units.

Oct. 22—Readmitted because of uncontrolled diabetes. B.M.R. plus 29 to plus 32. Weight 98 pounds. Hyperthyroidism still active. Additional x-ray therapy recommended.

Oct. 25—Thiouracil, 0.1 Gm. three times a day, substituted for Lugol's solution. First day of thiouracil therapy leukocyte count 2550, following day 2150. Thiouracil discontinued. Leukocyte count promptly returned to normal.

Nov. 1—Leukocyte count 4500. Thiouracil, 0.1 Gm. twice a day, started.

Nov. 11—Leukocyte count unaltered, dose increased to 0.1 Gm. four times a day.

Nov. 24—X-ray to thyroid, 1200 r.

Nov 29—B.M.R. plus 19, weight 109 pounds.

Dec. 1—Discharged on diabetic regimen and thiouracil, 0.1 Gm. four times a day. Diet unchanged, 160 units of protamine-zinc insulin and 150 units of crystalline insulin each morning required to maintain relative aglycosuria with fasting blood sugar level about 100 mg. per 100 cc.

Dec. 22—Pedal edema. Family physician discontinued thiouracil.

March 22—Patient well until two weeks previously. Symptoms of hyperthyroidism severe. Blood sugar levels: fasting, 148 mg. per 100 cc., and 102 mg. per 100 cc. after a meal. Insulin, 130 units protamine-zinc and 140 units crystalline. B.M.R. plus 59, weight 110¼ pounds, pulse rate 96 per minute. Lugol's solution, 1 cc. three times a day, and thiouracil, 0.6 Gm. a day, prescribed.

April 21—B.M.R. plus 25, pulse rate 100 per minute, diabetic control fair. Cardiac murmur, liver enlargement, and edema disappeared. Blood pressure 160/96. Diet unchanged. Insulin, 115 units protamine-zinc and 90 crystalline in morning. Leukocyte count 4450.

April 26—Thiouracil reduced to 0.4 Gm. a day and Lugol's solution to 10 minims a day. Diet changed: carbohydrate 300 Gm., protein 114 Gm., and fat 127 Gm. Insulin, 60 units protamine-zinc and 45 crystalline.

June 20—Lugol's solution discontinued.

Aug. 29—Leukocyte count 4900. B.M.R. plus 6. Pulse rate 64 per minute. Weight 126 pounds, a gain of 40 pounds.

In a recent communication the patient stated that she felt well, weighed 136 pounds, and was able to do her own housework.

Jan. 6, 1945 — Weight 136 pounds. B.M.R. plus 5. Symptom free. Insulin has been reduced to 20 units of crystalline and 25 of protamine-zinc a day, a total of 45 units as compared to a previous maximum of 300 units a day in November 1943.

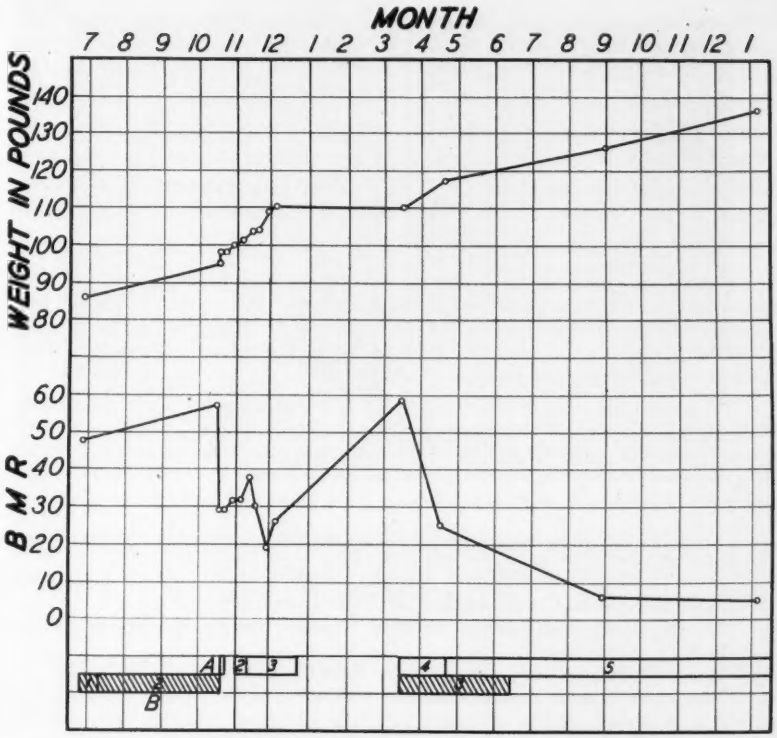



FIG. 1, Case 1. A. Thiouracil in Gm. (1) 0.3 (2) 0.2 (3) 0.4 (4) 0.6 (5) 0.4.
B. Lugol's solution in cc. (1) 3.0 (2) 0.3 (3) 3.0.

**Comment** This elderly woman with a large nodular goiter, severe hyperthyroidism, cardiac decompensation, and diabetes mellitus, who probably would not have survived operation, experienced a degree of improvement on thiouracil that would not have been expected on iodine alone. Although x-ray therapy may have been beneficial, the sustained improvement was not due to this as was demonstrated by the pronounced rise in basal metabolic rate that occurred three months after thiouracil was discontinued. Improvement was slow but definite. The slowness of the response may have been exaggerated by the long continued use of iodine. When first admitted to the hospital she was emaci-

ated and bed-ridden and had severe hyperthyroidism, diabetes, orthopnea, and edema. At present she is comfortable, well, and happy and is able to be as active as she wishes. If thyroidectomy had been possible, improvement might have been more rapid but could not have been more complete. It is fortunate that the drug was given a second trial after the first occurrence of leukopenia. Operation, which was considered and postponed repeatedly, finally seemed unnecessary. Whether improvement may eventually be maintained without thiouracil is not known but is not a matter of much importance.

**Case 2**—An Italian woman, aged 55, was seen on March 14, 1944 with the complaint of goiter, nervousness, and weight loss of 85 pounds in five months. She had been treated for cardiac decompensation. The goiter was first discovered five weeks previously during hospital treatment elsewhere for dropsy. She had taken Lugol's solution, 15 drops three times a day, for one month prior to admission.

The patient was quite thin. Her height was 62.5 inches and her weight 102 pounds. Möbius sign was present but no exophthalmos. The goiter was moderately large, rubbery, and slightly nodular. The radial pulse rate was 76 per minute and grossly irregular. Râles were present at the lung bases, and the heart was enlarged. The apical rate was 112. There was pronounced tremor of the hands and slight edema of the feet.

April 14—Admitted to the hospital. Risk of surgery considered prohibitive. Lugol's solution, 1 cc. three times a day, for seven days prior to admission.

April 15—Thiouracil, 0.6 Gm. a day, and digitalis prescribed. Iodine discontinued.

April 23—Thiouracil dose changed to 0.5 Gm. twice a day.

May 14—Discharged. Regimen including thiouracil, digitalis, and 4000 calorie diet.

May 19—Ankle edema.

June 9—Thiouracil decreased to 0.2 Gm. three times a day.

July 14—Thiouracil, 0.5 Gm. a day.

Aug. 4—B.M.R. plus 8.

Aug. 25—B.M.R. minus 13. Thiouracil reduced to 0.2 Gm. a day.

Sept. 15—B.M.R. plus 24. Thiouracil increased to 0.2 Gm. twice a day. Auricular fibrillation present, liver two fingers' breadth below costal margin, ankle edema still present.

Sept. 30—B.M.R. minus 1. Gland strikingly enlarged. In addition to thiouracil, 0.1 Gm. four times a day, thyroid, ½ gr. a day, given in an attempt to reduce vascularity of gland.

Oct. 7—B.M.R. plus 12. Thiouracil, 0.6 Gm., and desiccated thyroid, ½ gr., a day. Operation again postponed because of vascularity of gland, pronounced thrill, and loud bruit.

Oct. 13—Discharged on regimen of thiouracil, 0.2 Gm. three times a day, and desiccated thyroid, 1 gr. twice a day.

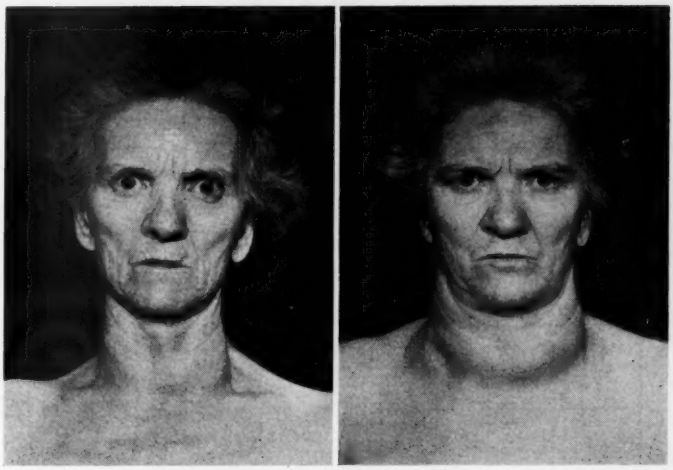
Nov. 3—B.M.R. plus 18. Patient taking thyroid, 4 gr. a day, by mistake. Thiouracil, 1.2 Gm. a day, desiccated thyroid, 4 gr. a day.

Nov. 10—Thiouracil, 1.0 Gm. a day of which 0.5 Gm. was taken, thyroid, 4 gr. a day. Gland still hypervascular with loud bruit.

Nov. 24—B.M.R. plus 31. Desiccated thyroid discontinued, and iodine (iodostarine), 10 milligrams a day, prescribed. Thiouracil, 0.5 Gm. a day.

Dec. 15—Patient in automobile accident on way to clinic. B.M.R. plus 12. Gland large and bulging symmetrically on each side of neck, more solid; thrill and bruit entirely gone.

Dec. 27—B.M.R. plus 4. Chronic leg edema present.



a b

FIG. 2, Case 2. (a) April 15, 1945, before taking thiouracil. (b) After taking thiouracil as shown in chart. Note increase in weight, disappearance of expression of anxiety and stare, and pronounced change in the size of the thyroid.

**Comment** Clinically the patient improved greatly during treatment with thiouracil, the improvement was slow, and the clinical condition did not approximate normal. After five months of treatment an attempt was made to maintain the improvement with a dose of thiouracil of 0.2 Gm. a day, but the basal metabolic rate rose quickly. Later an attempt was made to avoid using iodine and to reduce the extreme vascularity of the gland by feeding desiccated thyroid. Doses varying from ½ gr. to 4 gr. a day for thirty-four days failed to accomplish this. Discontinuation of thyroid medication and substitution of 10 milligrams of iodine a day was followed by rapid reduction in glandular vascularity and return of metabolic rate to normal.

**Case 3**—A woman, aged 50, was seen on May 25, 1944 because of goiter which was present for two years. Operation was advised elsewhere but refused. She was taking Lugol's solution, 5 drops a day, and tincture of digitalis, 15 drops a day.

Her face was thin, and she was in obvious respiratory distress. Height was 60 inches and weight 124½ pounds. The skin was cold and moist. There was severe exophthalmos and symmetrical, smooth enlargement of the thyroid gland. The heart was enlarged to the left anterior axillary line, and there was a low systolic apical murmur. Mild pitting edema of the ankles and legs was present.

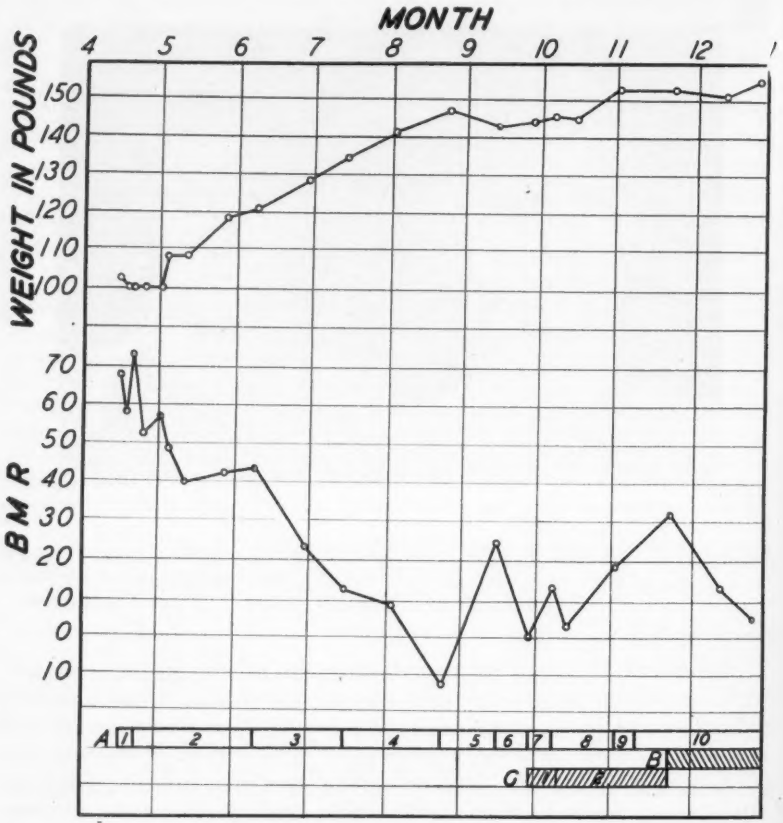



Fig. 3, Case 2. A. Thiouracil in Gm. (1) 0.6 (2) 1.0 (3) 0.6 (4) 0.5 (5) 0.2 (6) 0.6 (7) 0.4 (8) 0.6 (9) 1.2 (10) 0.5. B. Iodine — mg. of iodostarine. (1) 10.0. C. Thyroid in grains. (1) ½ (2) 4.

June 16—Admitted to the hospital for thyroidectomy. Operation postponed because of auricular fibrillation and cardiac decompensation. B.M.R. plus 58. Apical pulse rate 120 per minute, grossly irregular. Blood pressure 160/86. Cardiac condition improved under treatment, patient brought into compensation and discharged. Lugol's solution discontinued, iodine (potassium iodide), 5 gr. three times a day, begun.

July 10—Thiouracil, 0.2 Gm. three times a day. Iodine continued.

Sept. 18—Fibrillation still present. B.M.R. plus 22. Pulse rate 100 per minute. Weight 143 pounds. Patient appeared calm and greatly improved. Iodine discontinued.

Oct. 7—Leukocyte count 3950.

Oct. 11—B.M.R. plus 21. Pulse rate 104 per minute. Weight 144 pounds. Fibrillation still present. Ankles swollen, liver slightly enlarged. Right shoulder stiff and painful, motion restricted as in periarthritis frequently associated with hyperthyroidism. Otherwise, patient felt better than at any previous time during treatment.

Nov. 1 — Patient felt ill. Right shoulder and hand painful with considerable swelling of hand. Thyroid gland enlarged, no bruit. Leukocyte count 3150, 28 per cent neutrophils. Thiouracil discontinued. Patient admitted to the hospital. Lugol's solution, 1 cc. four times a day, prescribed, but only part taken. Fever and rash appeared. Iodine discontinued, rash subsided, appetite improved. B.M.R. plus 38. Pulse rate 100 per minute. Weight 124½ pounds.

Nov. 6—Lugol's solution discontinued.

Nov. 14—Discharged on thiouracil, 0.1 Gm. twice a day, plus digitalis.

DEC. 5—Patient felt ill. Losing weight, appetite poor. B.M.R. plus 54. Pulse rate 92 per minute. Leukocyte count 3800. Thiouracil dose increased from 0.2 Gm. to 0.6 Gm. a day.

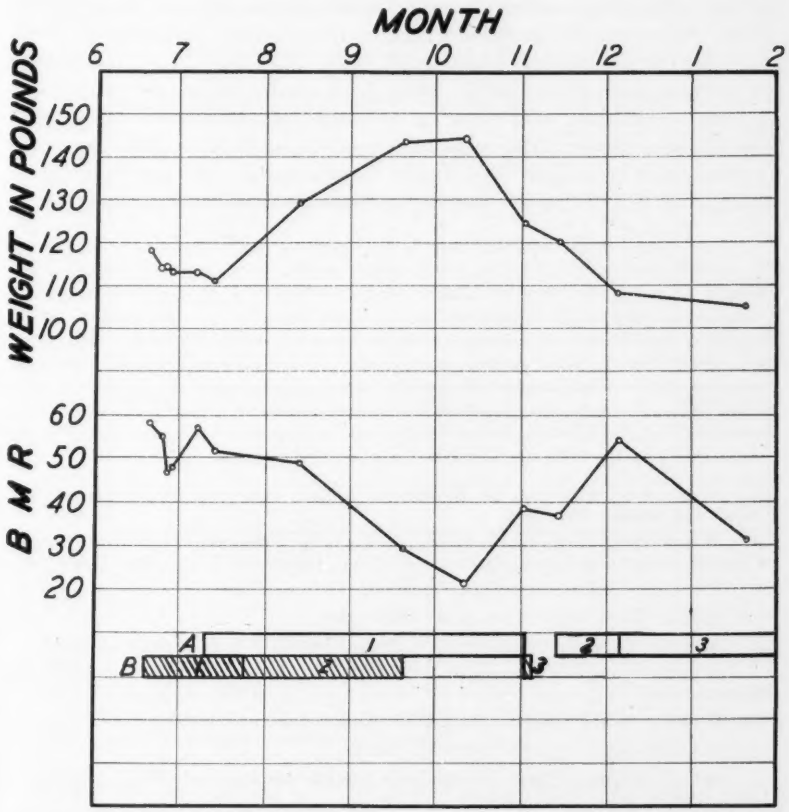



FIG. 4, Case 3. A. Thiouracil in grams. (1) 0.6 (2) 0.2 (3) 0.6. B. Iodine (1) and (2) 15.0 gr. potassium iodide. (3) 4.0 cc. of Lugol's solution.

Dec. 18—Patient confined to bed with decubitus ulcer. Shoulders less stiff and painful. Little evidence of hyperthyroidism. Slight but definite increase in size of goiter. No bruit nor thrill. Heart enlarged, soft systolic apical murmur and short aortic murmur. Pulse rate 67 per minute, regular. Treatment for ulcer recommended. Other treatment unchanged.

Jan. 20, 1945—B.M.R. plus 31. Weight 105 pounds. Leukocyte count 4300, 50 per cent neutrophils, 48 per cent lymphocytes, 2 per cent monocytes.

**Comment** The effectiveness of thiouracil was demonstrated in this case of hyperthyroidism in which operation was contraindicated. The patient improved strikingly for about one and one-half months, after which her general condition seemed to become worse, and the leukocyte count decreased. Progress was further retarded by periarthritis of the shoulder, by polynuclear leukopenia, which appeared dangerous enough to warrant withdrawal of the drug, and finally by iodine rash, fever, nausea, weight loss, and a rise in the basal metabolic rate. After many months of treatment the total improvement over her condition at the beginning of treatment was slight. Thiobarbital was prescribed in an attempt to obtain further benefit without undesirable side reactions.

**Case 4**—A woman, aged 62, came to the Ophthalmology Department on January 25, 1944 because of failing vision. Hemorrhagic retinitis was present. The patient was referred to the Department of Endocrinology on March 1. A diagnosis of diabetes mellitus was made on the basis of 4 plus urine sugar and a blood sugar level of 500 mg. per 100 cc. two hours after a meal. A nodular goiter was found. The pulse rate was 100 per minute, and the blood pressure was systolic 190 and diastolic 90 mm. of mercury. Hyperthyroidism was diagnosed. A smooth mass was palpated in the cul-de-sac of the pelvis. The patient was put on a diabetic regimen consisting of carbohydrate 190 Gm., protein 92 Gm., fat 100 Gm., calories 2118, and insulin, 30 units of protamine-zinc and 5 units of crystalline each morning. She was also given digitalis, 1.5 gr. daily.

March 6—B.M.R. plus 38. Weight 115 pounds. Pulse rate 88 per minute. Thyroidectomy advised but refused.

March 22—B.M.R. plus 39. Weight 115¼ pounds. Pulse rate 92 per minute. Because of clinical evidence of hyperthyroidism, placed on thiouracil, 0.2 Gm. three times a day.

April 12—Digitalis prescribed. Thiouracil, 1.0 Gm. a day.

May 5—Thiouracil, 0.2 Gm. three times a day.

May 15—Dependent edema present. Patient refused B.M.R. determination.

May 22—Condition unchanged. B.M.R. plus 40. Weight 120½ pounds. Pulse rate 92 per minute.

June 14—B.M.R. plus 35. Weight 123 pounds. Pulse rate 92 per minute.

June 23—Much improved. Gaining weight.

July 7—Edema of legs. Rumpel-Leede fragility test positive, 90-100 petechiae in 1 inch circle on arm. B.M.R. plus 49.

Aug. 9—Ankles, thighs, hands swollen. Face puffy. Dyspnea, loss of appetite, weakness. Insulin reactions. Thiouracil reduced to 0.4 Gm. a day.

Sept. 2—Admitted to hospital. Dyspnea, swelling of abdomen, feet, and ankles. Severe pain in lower back and thigh for five months. After few days of urinary incontinence, acute urinary retention developed.

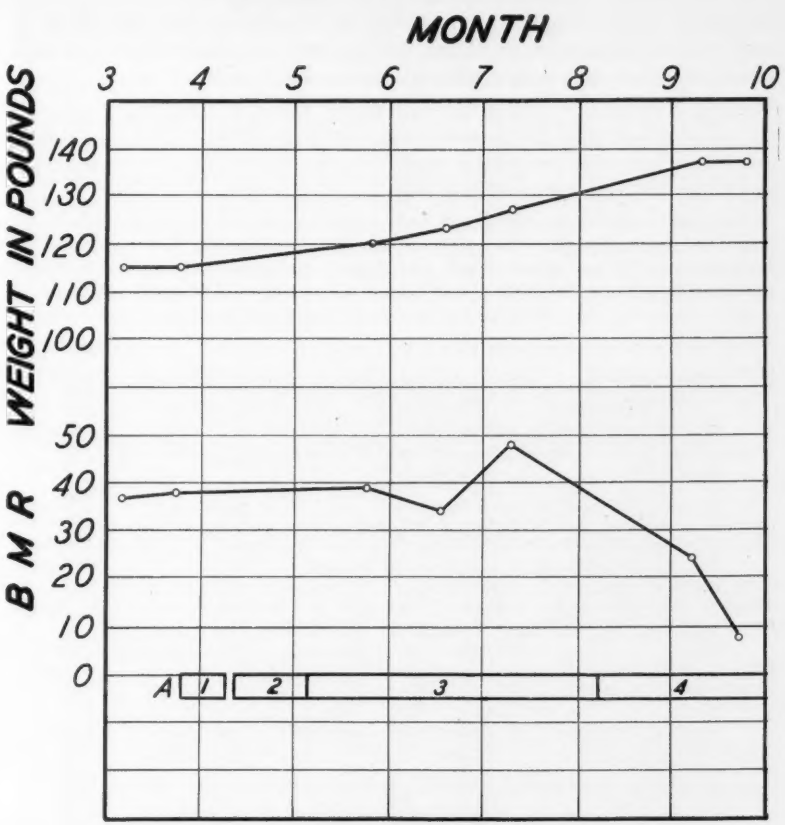



FIG. 5, Case 4. A. Thiouracil in Gm. (1) 0.6 (2) 1.0 (3) 0.6 (4) 0.4.

SEPT. 8—B.M.R. plus 24. Digitalis given. Diagnosis: pelvic tumor with questionable cord lesion, primary or secondary. Operation not considered possible.

SEPT. 22—B.M.R. plus 9.

SEPT. 30—Discharged on thiouracil, 0.4 Gm. a day, digitalis, 1½ gr. a day, bladder medication, supportive therapy, diabetic regimen.

**Comment** This patient had a nodular goiter, moderately severe hyperthyroidism, pelvic tumor, and diabetes mellitus. Operation was originally advised, but the risk would have been considerably greater than average because of cardiovascular condition. Later operation was not possible. Because of the poor cardiovascular condition and the grow-

ing pelvic mass, which was probably an ovarian tumor, she failed to show much improvement. That the hyperthyroidism diminished considerably in severity was evidently due to thiouracil.

**Case 5**—A woman, aged 56, was first seen on July 22, 1944 because of goiter. In the preceding two years she lost 80 to 85 pounds in weight. She complained of being nervous and hot and of having shaky hands. Stiffness of the knees and neck and generalized aching had been present for some time.

Physical examination revealed a well developed, obese woman, whose skin was warm and moist. Systolic blood pressure was 190 and diastolic 90 mm. of mercury. Pulse rate was 120 per minute. There was slight exophthalmos with some retraction of the upper lids. Both lobes of the thyroid gland were visibly and palpably enlarged, and a bruit was present over the gland. A soft aortic systolic murmur was heard.

A diagnosis of diffuse goiter with hyperthyroidism was made, and the patient was given Lugol's solution, 1 cc. three times a day. The basal metabolic rate was plus 81. Sedatives were ordered, and hospital care was suggested.

July 31—Pain in both shoulders. Severe limitation of motion. Diagnosis: periarthritis of shoulders. Analgesic medication given. B.M.R. plus 48.

Aug. 10—Much improved. B.M.R. plus 58.

Aug. 25—Shoulder pains increased. Pain and aching generalized. For thirty-nine days phenobarbital, ½ gr. three times a day, and Lugol's solution, 1 cc. three times a day. Medication continued, and heat applied to shoulders. B.M.R. plus 60. Hospital care urged.

Aug. 31—Severe shoulder pain caused sleeplessness. Pulse rate 130 per minute. B.M.R. plus 71. Hospitalization for treatment of periarthritis and hyperthyroidism. Given sedation, traction applied to arms. Diathermy and message refused. Improvement moderate, shoulder pain severe. Physical therapy discontinued.

Sept. 5—After Lugol's solution, 1 cc. three times a day, for fifty days, thiouracil, 0.6 Gm. a day, started. Patient restless and difficult to manage. Insisted on getting out of bed and fell frequently in doing so. Lugol's solution was discontinued for five days, then given again.

Sept. 25—Severely "toxic" appearance developed. Temperature rose rapidly to 106 F. and pulse rate to 150 per minute. Possibility of drug reaction prompted withdrawal of thiouracil. Condition continued critical. Despite oxygen and other supportive measures, entered acute thyroid crisis. Died.

Necropsy—Hypertrophy and dilatation of heart (460 Gm.). Acute portal inflammation and focal necrosis of liver. Healed nondeforming endocarditis of all four valves. Persistent thymus. Bronchopneumonia (terminal). Hypertrophy, hyperplasia, and multiple small adenomas of thyroid. Thyroid 205 Gm. Grossly firm, moderately friable, contained multiple circumscribed nodules 3 to 4 cm. in diameter. On cross section most tissue pale yellow. Microscopically follicles chiefly small but varied considerably in size. Acinar lining cells chiefly columnar, many of the secreting type. Acini contained colloid in varying amounts.

**Comment** This patient had severe hyperthyroidism with the late complication of very painful periarthritis. No improvement of consequence was produced by any of the treatment. In retrospect it must be questioned whether she might have been able to withstand operation if she had entered the hospital when first advised. Also the question might be asked whether the thiouracil action was obscured because of quantities of thyroid hormone stored in the gland during the iodine action, or whether the thiouracil effect was inhibited in some other way.

Perhaps it was used over too short a time to expect much effect. The severity of the hyperthyroidism was obviously an important factor and was made apparent by lack of response to iodine. The gland showed little of the hyperplasia commonly associated with a thiouracil reaction.

**Case 6**—A woman, aged 65, was first seen on March 2, 1944. She had been well except that her voice had become quite deep, and diagnosis of chronic laryngitis had been made. Vocal cord paralysis was not present. In December 1943, auricular fibrillation developed, and the basal metabolic rate was plus 42. A high basal metabolic rate was confirmed several times, readings as high as plus 55 being found. The patient was quite nervous. There was a mild diabetes readily controlled by diet. X-ray films taken elsewhere were reported to show a substernal goiter.

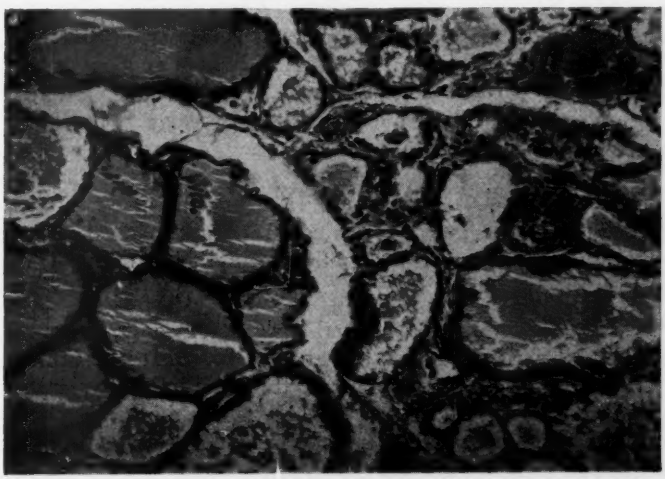


FIG. 6, Case 5. Relatively large amount of colloid in many of the follicles and virtually none of the evidences of hyperplasia commonly seen in the thyroid gland after treatment with thiouracil.

The pulse rate was 132 per minute. Auricular fibrillation was present. She had gained 10 pounds in weight, and pitting edema was present. The eyes were somewhat prominent, and there was a mild digital tremor. The patient had been given Lugol's solution for five days and thiouracil, 0.6 Gm. a day, for sixty-five days. No clinical improvement was apparent, although she gained about six pounds in weight, and the cholesterol level rose from 108 to 149 mg. per 100 cc. Lugol's solution, 5 minims a day, was recommended.

MARCH 22—Admitted to the hospital for possible thyroidectomy. No palpable thyroid enlargement. Height 65 inches, weight 138¾ pounds. Apical cardiac rate 104 a minute. Facial appearance suggested early acromegaly, but x-ray films of sella turcica reported normal.

Given digitalis, 1½ gr. a day; Lugol's solution, 1 cc. three times a day; and supportive therapy. B.M.R. plus 43. Electrocardiogram showed evidence of myocardial damage, auricular fibrillation, and digitalis effect. Diuretic therapy, mercuperin, and ammonium chloride instituted. Sedation. Placed on diabetic regimen: carbohydrate 190 Gm., protein 80 Gm., fat 200 Gm., and 15 units of protamine-zinc insulin daily.

March 28—B.M.R. plus 29. Weight 125 pounds. Pulse rate 46 per minute.

April 11—Became steadily worse. Ate poorly. X-ray therapy totaling 1200 r to thyroid gland.

April 25—B.M.R. plus 32. Weight 107 pounds. Pulse rate 80 per minute.

May 6—B.M.R. plus 31. Weight 108 pounds. Pulse rate 92 per minute.

May 10—Thiouracil, 0.4 Gm. a day.

May 12—Cerebral accident, right hemiplegia, coma.

May 13—Death.

**Comment** This is an example of apparent and unexplained failure of thiouracil. No improvement of clinical significance occurred while the patient took thiouracil for two months. It is interesting that there was also little or no improvement on iodine, which is also unexplained. Although the patient's course was steadily downhill, death never appeared imminent and apparently was due to a vascular accident. At no time was there reason to doubt the accuracy of the diagnosis. In retrospect it appears that the relative severity of the hyperthyroidism in this case was lessened. In other cases with large nodular goiter many months were required before the patient's condition approached normal, and continuation of thiouracil with patience might have lead to eventual control in this instance.

The facial appearance suggested early acromegaly, but x-ray films of the sella turcica revealed no evidence of tumor. It is possible but not likely that a pituitary factor similar to that seen in the hyperthyroidism of acromegaly may have been present. Whether this might constitute a reason for some difference in response from that seen in other cases of hyperthyroidism is not known.

## SUMMARY

These 6 cases of hyperthyroidism were selected because they demonstrate a wide range in response to treatment with thiouracil, varying from complete recovery in severe complicated hyperthyroidism to apparent total lack of response. All of these cases except one (case 5) were treated over many weeks or months. All were considered inoperable for one reason or another. In such cases any kind of treatment is at a great disadvantage, and where improvement is obtained with thiouracil, it may be considered greater than that possible with any other type of therapy. Various interesting facts are demonstrated by these cases. (1) Improvement in chronic severe hyperthyroidism may be very slow. (2) Pronounced enlargement of the gland with striking increase in

vascularity may occur. (3) In one instance the glandular vascularity failed to change materially during a month on thyroid therapy, but was quickly reduced with doses of iodine of 10 milligrams a day. (4) After as much as five months of treatment with thiouracil and a good response, the metabolic rate may rise rapidly with reduction of the dose to 0.2 Gm. a day. (5) In one case a mild leukopenia proved to be no contraindication to thiouracil, and recovery was the most complete we have seen with this drug. In one case moderately severe polymorphonuclear leukopenia occurred.

In summary the response in the various cases was as follows:

Case 1—Apparently complete control with rehabilitation.

Case 2—Considerable improvement without rehabilitation of the patient. However, although we did not see the patient before the onset of hyperthyroidism, her present condition probably approximates that prior to the present illness.

Case 3—Striking improvement was followed by polymorphonuclear leukopenia, severe iodine reaction, periarthritis, and exacerbation of the hyperthyroidism.

Case 4—Improved greatly so far as the metabolic rate was concerned, but clinical status remained poor largely because of factors other than hyperthyroidism.

Case 5—Died in thyroid crisis after iodine had been used for nearly six weeks. Thiouracil was given a trial of twenty days during which true crisis supervened.

Case 6—Little or no improvement on thiouracil for two months and none subsequently on iodine therapy. After resumption of thiouracil therapy the patient died suddenly from a cerebral vascular accident.

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# PARATHYROID ADENOMA TREATED WITH X-RAY AND SURGERY

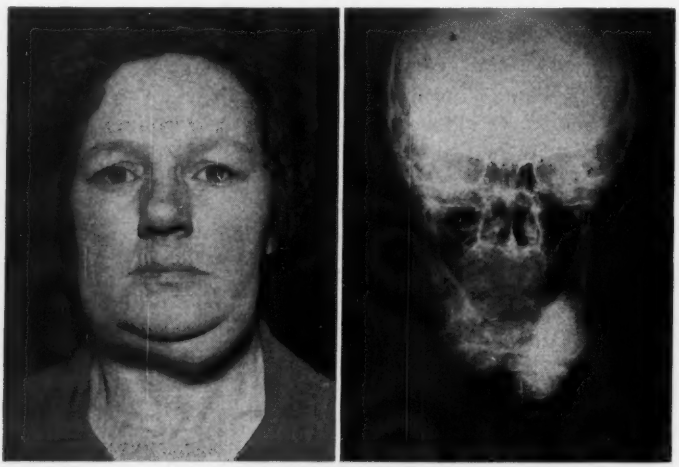
## *Report of a Case*

R. S. DINSMORE, M.D., AND E. ZIDD, M.D.

The purpose of this report is to present a case of parathyroid adenoma removed surgically after treatment elsewhere with x-ray. Although surgical excision is the commoner treatment of adenoma of the parathyroids, cases in which irradiation to the parathyroid region has brought about some improvement have been reported. Merritt and Lattman[1] reported seven cases in which irradiation produced not only symptomatic relief but also some regression of bone changes. However, it is possible that parathyroid lesions treated with x-ray may not be true adenomas. This case offered an opportunity to examine a true adenoma removed by excision after treatment with x-ray and to consider changes possibly produced in the gland by irradiation.

### CASE REPORT

A white woman, aged 40, was first seen on September 25, 1943. She complained of a lump in her jaw. In 1936 she noted a swelling in the left mandible, which slowly increased in size. In 1939 a tender tumor appeared on the right jaw, and the patient, who was an active, alert person, became lethargic and easily fatigued. In May 1940 she



a b

FIG. 1. (a) Photograph of patient demonstrating tumors of the mandible.
(b) X-ray showing bilateral cysts of mandible. There has been no change in these to date.

received an unknown amount of irradiation to the entire jaw and over the neck generally, and thereafter she thought that she was less drowsy.

In 1942 she became extremely nervous, irritable, and emotionally unstable and frequently had severe left frontal and parietal headaches, which continued until her admission to the hospital on November 2, 1943.

Physical examination revealed a well developed, well nourished woman with tumors of both rami of the mandible, more severe on the left. There was a scar over the left tumor at the site of an old curettement. Other physical findings were within normal limits.

Laboratory studies showed the urine to contain 15 to 18 pus cells per high power field. Hemoglobin was 74 per cent (Haden-Hausser), leukocyte count 5700, serum calcium 11.8 mg. per 100 cc., serum phosphorus 1.9 to 2.1 mg. per 100 cc., serum protein 5.8 Gm. per 100 cc., and serum phosphatase 1.7 units; Wasserman and Kahn tests were negative. X-ray film of the mandible revealed an expanding cystic lesion of both rami measuring about 4 by 7 cm. K.U.B. and pyelograms revealed calculi in the right kidney pelvis and gallbladder.

A diagnosis of adenoma of the parathyroid was made, and the patient's neck was explored.

At operation two parathyroid glands were found in each lobe of the thyroid. A lesion, which appeared to be an adenoma of the thyroid, was excised from the posterior

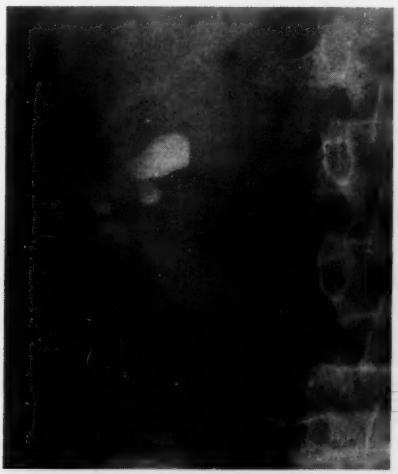


FIG. 2. K.U.B. showing calcification in right kidney.

lateral aspect of the right inferior lobe. The specimen measured approximately 1.5 cm. in diameter and had a thick, fibrous capsule containing small areas of calcification; the center had undergone partial cystic degeneration and contained soft brownish yellow tissue. Microscopic examination revealed this to be a partially degenerated parathyroid adenoma.

On the first postoperative day the serum calcium was 10.2 mg. per 100 cc. and the serum phosphorus 3.2 mg. per 100 cc. Chvostek's sign was present and Trousseau's sign absent. The patient complained of some tingling in both hands and feet and about the mouth. On the second postoperative day the serum calcium level fell to 9.0 mg. per 100 cc., and the serum phosphorus rose to 3.5 mg. per 100 cc. There was a moderate increase in severity of the tingling of hands and feet and in circumoral numbness, which was relieved by intravenous administration of 10 cc. of 10 per cent calcium gluconate. She required no further calcium therapy and made an uneventful recovery.

TABLE 1—Calcium, phosphorus, and protein levels of serum before and after operation.

| Date | Calcium | Phosphorus | Protein |
|---|---|---|---|
| 9-22-43 | 11.8 | 2.1 | |
| 11-3-43 | 11.0 | 1.9 | 5.8 |
| 11-8-43 | 11.8 | 2.0 | 5.8 |
| Operation | .... | ... | ... |
| 11-9-43 | 10.2 | 3.2 | 5.6 |
| 11-10-43 | 9.0 | 3.5 | 5.4 |
| 11-11-43 | 9.8 | 2.9 | 5.5 |
| 11-12-43 | 9.3 | 3.2 | ... |
| 11-13-43 | 10.0 | 3.2 | ... |
| 11-15-43 | 10.2 | 3.2 | ... |
| 11-16-43 | 10.6 | 4.3 | ... |
| 11-18-43 | 10.0 | 3.4 | ... |
| 11-19-43 | 10.5 | 3.1 | ... |
| 1-18-44 | 11.0 | 2.1 | ... |
| 1-20-44 | 10.7 | 2.5 | ... |

The patient made follow-up visits on January 20 and March 15, 1944. X-ray films showed no change in the kidney lesion or the bone lesions on the mandible. Subjectively she was improved. Symptoms present at hospital admission including headaches had disappeared. On March 15 she still noticed tingling of her hands and about the mouth and occasionally had some twitching of the left side of the face when excited, but later these disappeared.

## DISCUSSION

This patient presented a typical picture of hyperparathyroidism with definite cystic bone changes, urinary calculi, and lethargy and drowsiness. After irradiation the drowsiness disappeared, but symptoms of numbness, irritability, and emotional instability developed. After removal of the parathyroid tumor all these symptoms disappeared.

Grossly the adenoma resembled a degenerated thyroid adenoma, presenting areas of fibrosis, calcification, and partial cystic degeneration. It is a matter for speculation whether or not these degenerative changes were secondary to x-ray therapy.

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# NODULAR PAPILLOMATOUS BROMODERMA

EARL W. NETHERTON, M.D.

Bromides are prescribed more often than many other common drugs and are also ingredients of many proprietary preparations. However, nodular, papillomatous, fungoid bromoderma is relatively uncommon. This type of bromide eruption occurs most often in women. The lesions usually appear after weeks or months of continuous bromide ingestion. There is no correlation between the amount of drug ingested, duration of medication, and onset of the eruption. The nervous and psychic manifestations of brominism may be present but are often absent. Likewise, constitutional manifestations of brominism may occur without an associated papillomatous bromoderma. A history of ingestion of bromide or sedatives is an important aid in the differential diagnosis. It should be pointed out, however, that a habitué of proprietary sedatives is often reluctant to admit ingestion of drugs.

If the practitioner is unfamiliar with this lesion, he is most apt to consider it a carbuncle or some unusual pyogenic infection and may subject the patient to a needless operation. The most striking feature of this type of bromoderma is the high incidence of severe pain and tenderness of the lesions. The patient frequently walks with a limp and may come to the physician's office on crutches. The pressure of bandages and clothing causes discomfort, although occasionally pain is not a prominent symptom.

A painful, nodular, papillomatous, pustular lesion not surrounded by acute cellulitis should indicate the necessity for considering bromoderma in the differential diagnosis. The initial lesion is a small, light red to yellowish red papule or group of painful papules. These papules become papulopustules, enlarge slowly by peripheral extension, may become confluent, and terminate in large, rounded or oval, irregular, fungoid or papillomatous, raised lesions. Usually the margins of the larger lesions are rather sharply demarcated and are surrounded by a narrow zone of erythema. During the early and more active stage of development the surface of the lesions is studded with small pustules. The exudate has a foul odor. As the pustules dry up, comedo-like plugs form, or if the pus is expressed, numerous small sievelike depressions remain on the surface of the lesion. This results in a cribriform appearance of the surface characteristic of this type of bromoderma. Scarring and hyperpigmentation are common sequelae of nodular bromoderma.

Areas of predilection are the lower anterior and lateral surfaces of the legs. Large fungoid and nodular lesions of bromoderma sometimes

occur in nursing infants whose mothers are taking bromides, and in the child the lesions show a predilection for the face and extremities. The eruption is usually bilateral, although it may be unilateral. It may consist of one or many large fungoid lesions with a few smaller papulopustules, or it may be extensive with numerous lesions. In most cases observed at the clinic the eruption consisted of few lesions. The papillomatous type of bromoderma not infrequently develops at the site of trauma.

Fungating nodular bromoderma must be differentiated from blastomycosis cutis, late nodular syphilid, tuberculosis verrucosis cutis, dermatitis vegetans, and carcinoma. Of these diseases blastomycosis most closely simulates papillomatous bromoderma. The margins of lesions of cutaneous blastomycosis are more sharply demarcated and more perpendicular. The abscesses are smaller and located along the rolled sharp margins. The surface of blastomycosis is more papillomatous and in the moist type bleeds easily. The exudate from bromoderma has a more offensive odor and does not contain the budding forms of blastomyces. Lesions of blastomycosis are not usually painful.

The nodular serpiginous margin of a bromoderma may simulate roughly that of late syphilid. The syphilid is of duller color and consists of a granulomatous infiltration which involves the whole thickness of the skin. The punched-out marginal ulcers and the atrophic scar with an areola of hyperpigmentation usually present in the older portion of a late syphilid do not occur in bromoderma.

Lesions of tuberculosis cutis are usually more verrucose, more chronic, less painful, and usually not so purulent. Likewise the margins are infiltrated and granulomatous.

Dermatitis vegetans is a rare, chronic, purulent, vegetating process, which usually involves the folds of the body, particularly the genitocrural regions and axillae. Occasionally a vegetating, papillomatous, pyogenic dermatitis involving the legs may roughly simulate a bromoderma; however, the presence of painful papulopustules and nodules is an important and distinctive characteristic of bromoderma.

Although a dry papillomatous area of a chronic bromoderma may simulate carcinoma cutis, the possibility of this error in diagnosis would be obviated if the whole eruption were carefully evaluated, since bromoderma does not tend to undergo malignant degeneration.

Prompt relief of pain and the rapid involution of the lesions after the administration of sodium chloride are observed in bromoderma and not

in the other lesions mentioned. In the clinical investigation of doubtful cases microscopic examination of the exudate and other well known laboratory procedures should be utilized.

Sodium chloride therapy for bromoderma advocated by Wile and his associates is exceedingly satisfactory and one of the most outstanding contributions to dermatologic therapeutics by contemporary dermatologists.[1, 2] Untreated bromoderma subsides slowly, often requiring weeks to disappear after bromide ingestion has been discontinued.

The presence of bromine in the urine or a high bromine blood level, although not conclusive, is strong supportive evidence in doubtful cases of bromoderma. A satisfactory method of determining the bromine level of the blood serum is now available and is more valuable than examination of the urine for bromine.[3, 4] Wile emphasized that bromine cannot always be found in the urine of patients with brominism until after the administration of sodium chloride.[2] He also cautioned against the production of nephritis by too rapid displacement of bromine by administration of large amounts of sodium chloride.

## CASE REPORTS

**Case 1.**—A woman, aged 45, came to the clinic because of an "ulcer" on the left leg. During the past year she was depressed and cried easily. During the past six months she lost 15 pounds. For three years she suffered from hot flashes and during the past year menstruated only three times. Six weeks prior to admission a painful red papule developed on the calf of the left leg, according to the patient at the site of a mosquito bite. The lesion gradually enlarged and became more painful, and a dark area developed at the apex. No pus was obtained upon incision, after which the lesion enlarged more rapidly, and small pustules appeared on its surface. Two roentgen ray treatments were given without benefit. The lesion continued to enlarge and became so painful that the patient was unable to walk without crutches.

Since cultures of exudate showed pure growth of Staphylococcus albus, wet dressings of allantoin solution were applied, after which the lesion became more painful and the erythematous areola more prominent. Because of lack of response to treatment, her surgeon attempted to prevent spread of the "infection" by producing an elliptical incision with the cautery needle around the lower, more rapidly advancing portion of the lesion. An iodoform pack was placed in the incision. At the same time a smaller, painful papulopustule on the upper left calf was excised.

A few days later she was seen in the department of dermatology. A dime-sized, clean, superficial ulcer involved the upper portion of the left calf. This was a postoperative wound. Lower on the lateral and posterior surface of the same leg was an irregular, papillomatous, vegetating, pustular lesion, about the size of a silver dollar and surrounded by a zone of erythema. The margin was raised, sloping, and fairly well demarcated. The peripheral portion was papillomatous and in places studded with small pustules. No part of the surface was cribriform. The central portion was brownish red, depressed, and scarred. There was a gaping, elliptical incision below the lesion (fig. 1).

The pain was severe, and the slightest pressure or movement caused discomfort greater than would be warranted by the appearance of the lesion.

A clinical diagnosis of bromoderma was made. When questioned about ingestion of sedatives, the patient promptly admitted taking a proprietary preparation containing

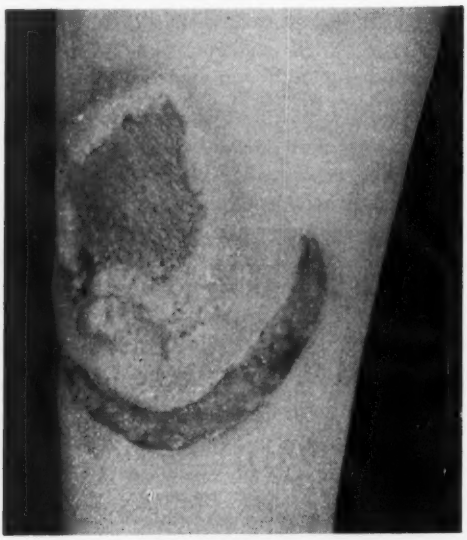

FIG. 1

sodium and potassium bromide. In fact she produced a bottle of the remedy during the interview. Examination of the urine by the Belote technic showed the presence of bromine. Wassermann and Kahn reactions of the blood were negative. Other laboratory investigations showed normal findings.

Within five days after intravenous administration of decinormal saline the pain completely disappeared, and within three weeks the lesion healed.

**Case 2.**—A woman, aged 43, came to the clinic on November 13, 1942 because of a painful lesion on the right leg. For the past eighteen months she had been taking a brown, salty liquid for "nervous exhaustion." In July she scratched the lateral surface of the right leg on a rosebush. Within a week a papule developed at the site of the injury, became very painful, and continued to enlarge slowly until she came to the clinic. During the last week of October a group of painful papulopustules developed on the midportion of the right antetibial area. The eruption was treated with moist dressings, sulfathiazole salve, and about eight roentgen ray treatments, none of which was beneficial.

There was a rounded, palm-sized, raised, light red, crusted, pustular, poorly demarcated, very painful lesion on the lateral surface at about the junction of the middle and the lower third of the right leg. A narrow erythematous areola surrounded the lesion. The crusts were yellowish, thin, and loosely adherent. On the noncrusted surface

were small pustules. The newer lesions on the right shin consisted of a group of pea-sized, light red, tender papules and papulopustales (fig. 2). The patient was restless, emotionally unstable, and complained of the painfulness of the cutaneous lesion. A diagnosis of bromoderma was made.

The bromide level of the blood serum was over 100 mg. per 100 cc. The patient lived out of the city and did not wish to remain for intravenous saline therapy. One gram of sodium chloride in enteric coated pills was administered orally four times a day. The nerve sedative was discontinued. Response to treatment was entirely satisfactory but was not so prompt as with the use of the intravenous administration of saline.

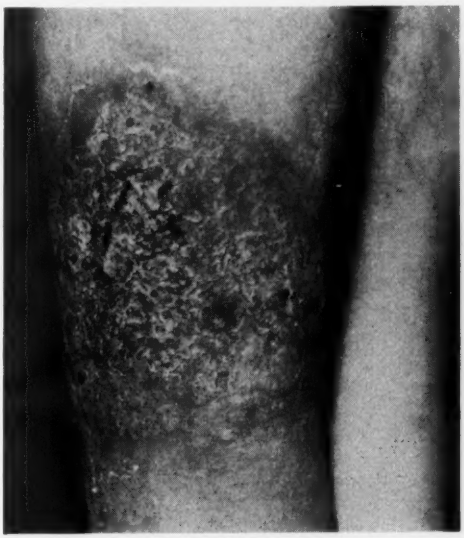

FIG. 2

**Case 3.**—A married woman, aged 32, was seen in August 1941 with the chief complaint of "sores" on the right leg of fifteen weeks' duration. She was neurotic and according to the referring physician was difficult to manage. She denied taking bromides but had taken phenobarbital for several years. Her physician had not prescribed bromides. The eruption had appeared as a small, crusted, pustular lesion on the right shin shortly after shaving the legs. The lesion enlarged gradually by peripheral extension and was tender but not painful. It was thoroughly curetted in June but returned within ten days and became larger.

On the midportion of the right antetibial region was a palm-sized, oval, well demarcated, chronic inflammatory lesion. The central portion was pink, depressed, and scarred. The periphery was papillomatous, pustular, and partially covered with brown, seborrheic, loosely adherent scales. The pustules were small. The margin of the lesion was raised but not sharply above the normal skin. There was an erythematous areola. The youngest papillomatous, fungoid nodule was confluent with upper lateral portion

of the original lesion. A similar quarter-sized lesion was present below and to the right of the original plaque (fig. 3).

Both blastomycosis and bromoderma were considered tenable in the differential diagnosis. Although the clinical features were more suggestive of bromoderma than blastomycosis, the lack of extreme tenderness and pain commonly present in bromoderma was confusing. Repeated examination of smears from pustules failed to demonstrate blastomyces, and cultures failed to grow the fungus. Despite the denial of bromide ingestion a blood serum bromine level was determined and showed 91 mg. bromine in 100 cc. of blood serum. The Wassermann and Kahn reactions of the blood were negative.

A final diagnosis of bromoderma was made, and the patient returned to her physician for saline therapy. No subsequent follow-up was obtained.

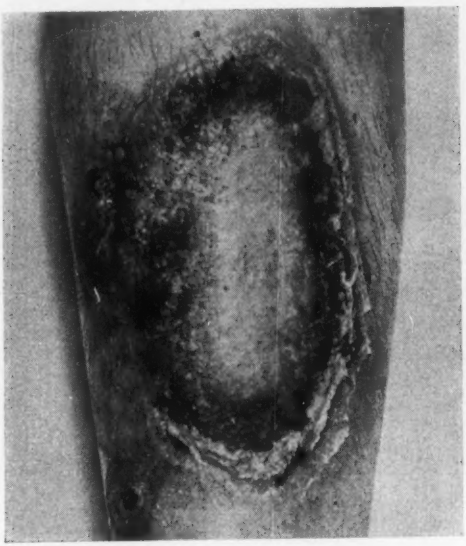

FIG. 3

**Case 4.**—A woman, aged 59, came to the clinic on March 17, 1938 because of a very painful eruption on the lower right leg. In 1933 she bruised the right shin, and within a week an exceedingly painful, red area appeared at the site of the injury. A large, very painful, pustular and crusted area developed on the anterior surface of the right leg, and a few months later a similar eruption appeared on the lower part of the left leg. After about two years the eruption disappeared leaving hyperpigmented scars. In April 1937 she again injured the right shin, and in a few days painful lesions similar to those that developed in 1933 appeared near the injury. The eruption spread, and the pain became so severe that she remained in bed most of the time from August 1937 to January 1938. She had a poor appetite, was nervous, and had frequent fainting spells. About the middle of February 1938 she injured her right leg again. Large bullae developed, and within three days the eruption spread to encircle the leg just above the

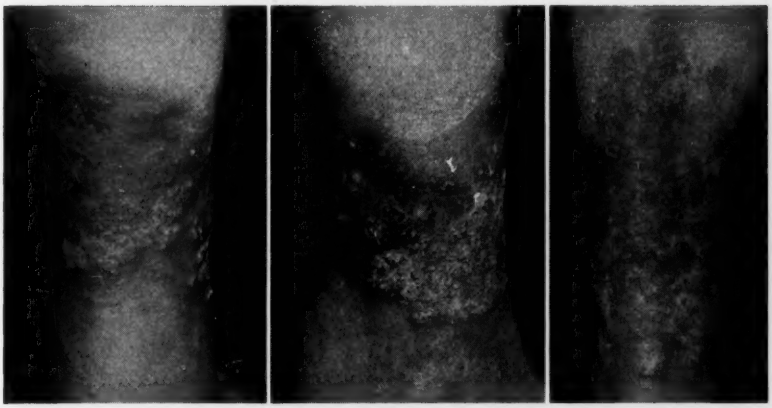

FIG. 4

ankle. The pain was severe, and the odor of the purulent exudate became offensive. During the past ten years she took a great deal of medicine, including proprietary preparations for stomach trouble, but denied taking any medicine for about five months before she came under our care. During September 1937 she took white tablets but did not know what they contained. History of drug ingestion in this case was confusing and unsatisfactory.

The eruption, which encircled the right leg just above the ankle and involved a hyperpigmented scar on the right shin, consisted of light red, vegetating, papillomatous nodules and erythematous areas studded with small pustules and match-head to pea-sized papulopustules. The nodular, more papillomatous portions of the eruption were sharply demarcated, but the margins were sloping. There was a narrow areola of erythema (fig. 4). The eruption was exceedingly painful, and the exudate had an offensive odor.

The Wassermann and Kahn reactions of the blood were negative. Cultures for blastomyces failed to grow any fungus. The blood bromine level could not be obtained, and the urine was not examined. Although the history of drug ingestion was not satisfactory, it was determined that she suffered from fainting spells, chronic stomach trouble, and other vague complaints, and that for years she had taken medicine periodically and at times regularly for several months. The nodular, vegetating, pustular, exceedingly painful eruption and the offensive odor of the exudate were sufficiently characteristic to permit a clinical diagnosis of bromoderma. After two intravenous injections of normal saline solution the pain decreased, and the patient returned to her family physician for further saline therapy.

## COMMENT

Bromine may cause an acneform eruption, erythema nodosum-like nodules, an erythematous vesiculo-bullous dermatitis, or papillomatous, nodular, fungoid lesions. The latter type of bromoderma is rather un-

common. Papillomatous bromoderma may at times be treated surgically before the exact nature of the lesion is recognized. This occurred in two of the cases herein reported. In a discussion of a case of bromoderma presented before the New York Dermatological Society, Traub referred to a woman who had extensive bromoderma on the legs.[5] One of the granulomatous tumors was diagnosed as malignant degeneration. Amputation of the leg was advised but was refused by the patient. After the eruption was identified and sodium chloride was administered, the lesions disappeared completely. In the same discussion Whitehouse cited two similar cases in which amputation of a leg was advised because of an erroneous diagnosis of sarcoma.

Unlike most drug eruptions the lesions caused by bromine and iodine do not disappear quickly after the drug is withheld. Prior to the outstanding contribution of Wile, Wright, and Smith there was no satisfactory treatment for bromoderma, consequently the fungoid cutaneous lesions caused by bromine would often last weeks or months after the ingestion of the drug had been discontinued.[1] These authors were able to corroborate observations of Laudenheimer, von Wyss, and others, whose researches demonstrated that the ingestion of bromide led to a gradual accumulation of the drug in the tissues and fluids of the body, caused by displacement of chlorine by bromine. Because of this phenomenon Laudenheimer attempted to explain the systemic symptoms of brominism as a manifestation of chloride deficiency. Wile and his associates were able to substantiate Laudenheimer's assumption by showing that introduction of large amounts of chloride was followed by gradual return of the normal chlorine content of the tissues and body fluids, relief of symptoms of brominism, and beneficial effect upon bromodermas. They also found that the normal chlorine content of the urine must be determined for each patient. With the ingestion of bromide the chlorine content of the urine began to increase on about the second or third day and continued to increase up to about twice the normal level; then there was a gradual return to normal even though the drug was continued. The normal chlorine level of the urine was not reached until after the drug was withdrawn. They were unable to demonstrate bromine in the purulent exudate of bromoderma or a sensitization to iodides and bromides by intracutaneous and scarification tests. They stated that "The local phenomena of iododerma and bromoderma do not find their explanation on simple bacterial nor simple chemical grounds. The ultimate explanation probably lies in a complex biochemical reaction. The classification of such cutaneous phenomena, however, as true sensitization or allergy is as yet unjustifiable in the light of present

knowledge." Two decades have passed since the article of Wile and his associates was published, and, so far as I have been able to determine, the mechanism of the production of iododerma and bromoderma remains obscure.

In a second report Wile confirmed this early observation.[2] He treated three women who presented the mental symptoms of brominism together with nodular bromide lesions of the skin by the administration of decinormal saline solution at two and three day intervals. Although bromine could not be demonstrated in the urine prior to the administration of saline solution, it was present after the first two injections. Likewise mental symptoms were promptly relieved with diminution and gradual disappearance of the cutaneous lesions. In the first case treated symptoms of shock developed almost immediately after administration of 500 cc. of decinormal saline solution intravenously. The next day a catheterized specimen of urine contained many casts and large amounts of albumin. Wile attributed these reactions to the irritating effect of the rapid production of chemical changes in the tissues and the rapid liberation of bromine with the passage of the bromine salt through the renal epithelium. He later cautioned against rapid liberation of bromine from the tissues by too extensive saline therapy.

Belote described a simple color test for bromine in body fluids as follows:[6] To urine suspected of containing bromine is added a few crystals of potassium permanganate. The urine is agitated, and a few drops of concentrated sulfuric acid is added. Small pieces of dried filter paper previously soaked in a saturated solution of fluorescein in 60 per cent acetic acid are moistened with 2 per cent acetic acid and held over the mouth of the test tube containing the urine, potassium permanganate, and sulfuric acid. If bromine is present, the yellow paper becomes bright pink.

## SUMMARY

The frequent ingestion of bromides in prescribed medication and proprietary preparations occasionally causes an eruption, which must be differentiated from blastomycosis cutis, late nodular syphilid, tuberculosis, verrucosis cutis, dermatitis vegetans, and carcinoma. Until Wile and his associates showed that the intravenous administration of decinormal saline solution caused the rapid disappearance of the lesions, there was no satisfactory treatment for bromoderma, which would often persist for weeks or months after the ingestion of the drug was discontinued. Recognition of papillomatous bromoderma will prevent surgical interference to which these lesions are at times subjected.

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# PARIETAL NEURALGIA

R. H. McDONALD, M.D.

Pain referred to a cutaneous area is one of the commonest complaints heard in any diagnostic clinic. When the reference of pain is over the thorax or abdomen, it is our common habit to think of the possibility of some visceral pathologic state, which, by means of a nervous connection involving the spinal cord, refers itself to the cutaneous surface. The reference of visceral pain through the efferent nervous connections to the spinal cord and its spread therefrom to the cutaneous sensory area supplied by the same cord segment or even to adjoining segments, if the stimulus be of sufficient intensity, has been suggested by the work of McKenzie[1], Head[2], and Sherren[3] and has found wide acceptance throughout medical literature. These cutaneous zones of somatic reference have been described on the basis of embryonic development and charted with a view to their use in diagnosis. Practically, however, it has been shown that they are of relatively little value, and constant relationships between visceral pathologic states and cutaneous manifestations have not been consistent. In general the principle still holds that clinical investigation must first envision the possibility of such an origin of pain, to be excluded only after the most thorough search. Frequently the most careful search will fail to uncover any such visceral basis, and in these the possibility of pain of parietal origin must be considered. Failure to appreciate the possibility of parietal origin for distress may lead to an unwarranted diagnosis of visceral disease with the sequelae of needless surgical procedures. Repeated examples of this, usually in the abdominal area, are commonplace, and this frequently explains the persistence of symptoms after repeated surgical attempts for relief. Such patients are frequently regarded as being

neurotic or having painful scars, neuromas, or aponeurotic strains. Frequently the persistence of symptoms after operation has been explained by that "last refuge of the diagnostically destitute, adhesions."

Parietal neuralgia may simulate a more deep seated disease in any part of the body. Clinically it is usually confined to the spinal nerves, since these emerge from the spinal canal through relatively small openings, the intervertebral foramina, and are therefore more subject to mechanical irritations, which provide the basis for the neuralgia. Thus the upper cervical nerves supply sensation to the occipital and mastoid areas and are frequently confused with pathologic processes in the mastoid cells, within the cranium, or in the nasal accessory sinuses. The lower cervical nerves supply sensation to the shoulders and arms. Owing to the absence of underlying viscera there is likely to be less confusion in the recognition of the signs of brachial neuralgia.

The intercostal nerves supply the chest wall, and intercostal neuralgia may simulate cardiac, pleural, and pulmonary disease. The anastomosis which exists between the lateral cutaneous branch of the second and sometimes the third intercostal nerve and the medial brachial cutaneous nerve in the axilla gives rise to the possibility of intercostal neuralgia being referred to the arm. This may, therefore, increase the suspicion of anginal pain raised by pain in the chest. The lower intercostal nerves supply the greater portion of the anterior abdominal wall, and in this area parietal neuralgia probably assumes its greatest importance, since it may simulate pathologic conditions in the gastrointestinal and the genitourinary tract. There is a tendency among physicians and surgeons to think first of the possibility of some abdominal origin for pain referred to the abdominal parietes, particularly since some surgical procedure may be necessary and life-saving. This must be considered the correct attitude, and intra-abdominal lesions which necessitate immediate surgery must not be overlooked. Parietal neuralgia certainly will never cause a fatality as appendicitis may, but on the other hand care must be taken to avoid unnecessary operations and to recognize that many of these pains are merely parietal in origin.

The upper lumbar nerves supply the skin sensation of the groin and mons pubis as well as the upper thigh, and this pain reference must be kept in mind in differentiation of pathologic conditions involving the bladder, lower bowel, and inguinal canal. Pain referred to the thigh and leg from the lower lumbar and sacral segments of the cord is less likely to be misinterpreted, as is pain referred to the upper extremity.

Parietal neuralgia is induced in the great majority of cases by some

pathologic process or by pressure upon the spinal nerve root, usually at the point where it emerges from the intervertebral foramen. The commonest cause in older patients is undoubtedly a hypertrophic arthritic process of gradual encroachment upon the foramen. In younger patients the question of postural strains must be considered. Structural scolioses, injuries and tumors of the bone may be readily recognized, but functional scoliosis may escape notice. This will only be seen by careful examination of the patient's back and posture. Any complete physical examination must include careful observation of the patient's back, preferably with the patient standing in his bare feet. Occasionally the neuralgia may result from irritation of the nerve along its course by tumor, aneurysm, or some mechanical irritation such as occurs in the scalenus anticus syndrome. In a few instances the factor would appear to be a toxic one, such as occurs in segmental neuralgia associated with upper respiratory infection. Pain associated with herpes zoster and tabes dorsalis must also be kept in mind.

Parietal neuralgia is likely to be of a dull chronic character, although more severe grades are encountered sufficient in degree in some instances to suggest an intra-abdominal emergency. The pain may be of fleeting duration, and this probably accounts for the transient pain which many normal individuals experience frequently and dismiss without consideration. To the person of neurotic temperament, however, this may assume major proportions. It must be remembered that pain is a subjective symptom and varies greatly between individuals. Tenderness in the parietal wall is always associated with the pain, and, as pointed out many years ago by Carnett[4], this must be differentiated from deep abdominal disease by making the examination with the abdominal wall tense. Tenderness with the abdominal wall in a tense state suggests the parietes as the location, provided that the parietal peritoneum is not inflamed. Tenderness with the abdominal wall relaxed may be in the parietes or in the underlying abdominal viscera. Hyperesthesia in the segmental area involved may also be noted and can be demonstrated by pinching the skin or by the reaction to a sharp point. Frequently a definite line of demarcation can be made by drawing a sharp point downward over the skin surface and asking the patient to note the level at which the stimulus appears to increase. The area of tenderness is usually larger than the area referred to as the site of pain and often overlaps portions of the chest and abdomen or the abdomen and thigh. Such a distribution of tenderness or of pain and tenderness over an area supplied by one or more cutaneous nerves and not overlying any definite viscus is especially suggestive of parietal neuralgia. Rigidity does not usually occur in parietal neuralgia, since only the sensory fibers are

ordinarily involved. Frequently in parietal neuralgia of the thoracic area it is possible to demonstrate considerable tenderness along the course of the nerve in the intercostal spaces by pressure, particularly near the spine.

A careful physical examination is essential. The habitus of the patient should be considered, since postural strains are more likely to occur in the linear asthenic type of individual. The general posture should be observed as well as the anteroposterior and lateral curves of the spine, and the legs should be measured for inequality of length. Flexibility in all directions should be checked carefully and tender points in the spine searched for by deep pressure with the knuckles. X-ray studies of the spine will frequently reveal arthritic processes and actual bony diseases if present. Inasmuch as parietal neuralgia is to a large extent a diagnosis of exclusion, all other methods which would seem to aid in diagnosis should be employed.

Abdominal wall tenderness may be eliminated by nerve blocking, which is, therefore, a useful measure in differentiating abdominal disease and pain of parietal origin. This may be carried out paravertebrally in the course of the thoracic and lumbar nerves or along the course of the nerve as in the case of the ilioinguinal nerve. In some instances local infiltration above the area of tenderness may be of diagnostic value. If tenderness on deep pressure can be eliminated by cutaneous anesthesia, it would seem likely that the pain has been of parietal origin.

Treatment of parietal neuralgia depends upon the process which has caused it. In the arthritic patient the use of heat and massage over the affected area will be of value. Limitation of the movement of the spine by adequate braces may be useful, and x-ray therapy to the spine has apparently been beneficial. Avoidance of prolonged walking and standing and a period of recumbency in a firm bed may be useful from a therapeutic viewpoint and also as an aid in diagnosis. In the case of younger persons, especially those of asthenic type, the use of graduated postural exercises is of chief importance. By their use muscle tone is improved, and ligamentous strain is relieved. Marked improvement of peripheral circulation is frequently seen in association with deep breathing exercises, and an improved position and circulation of the abdominal viscera often alleviates the indefinite gastrointestinal symptoms of which these patients complain. A short lower extremity may be corrected with a lift in the heel sufficient to cause the pelvis to be level and to restore the symmetry of the spine, thus overcoming the mechanical basis for strain. Adequate rest is also beneficial and may be all important in the chronically exhausted individual.

SUMMARY

Parietal neuralgia must be considered in the differential diagnosis of dull persistent pain referred to any cutaneous area. It is particularly to be considered when the findings are not suggestive of some clean cut, deep seated pathologic process. It is in general an elimination diagnosis, only to be advanced after careful search for other possible causes. It may simulate a great variety of other conditions and is undoubtedly responsible for many tentative diagnoses of pleurisy, gallbladder disease, kidney disease, and spastic colon for which adequate evidence cannot be advanced. Relief depends upon the recognition and correction as far as possible of the basic pathologic processes. Of chief importance is its differentiation from conditions requiring operation.

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# TREATMENT OF ACTINOMYCOSIS WITH PENICILLIN

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Two cases of actinomycosis satisfactorily treated with penicillin are reported. Lyons[1] reported improvement in 4 cases treated with penicillin but stated that a longer follow-up period was necessary. Herrell[2] treated a case of abdominal actinomycosis complicated by carcinoma of the colon with unsatisfactory results. In 3 cases of maxillofacial actinomycosis he considered recovery satisfactory. Florey and Florey[3] believed that in their 2 cases dosage was inadequate. Christie and Garrod[4] treated a patient with actinomycosis of the chest wall and lung, who subsequently died from infection introduced by penicillin intravenous drip. At autopsy they observed disintegration of the fungus colony, which they believed might have resulted from treatment.

## CASE REPORTS

**Case 1**—The patient was a white woman, aged 44. She was admitted to the hospital in May 1944. In January 1943 a supracervical hysterectomy was performed in another hospital. Soon after operation abscesses and multiple fistulas developed. X-ray showed a communication between one fistula in the lower left abdomen and the small bowel and vagina. A second sinus draining from the left iliac region and a third from the lower right chest wall did not communicate with a viscus.

For sixteen months prior to penicillin treatment, the patient had a slight temperature elevation daily, was unable to be out of bed, lost weight, and had no appetite, and the sinus tracts drained pus continually. The pus contained sulfur granules and actinomyces. The patient was hospitalized and during a thirty day period received a total of 2,000,000 units of penicillin by intramuscular injection of 15,000 units every three hours. The sinuses were irrigated with a 5 per cent penicillin solution four times daily. She gained 30 pounds, regained her strength and appetite, and was ambulatory when discharged from the hospital. The temperature returned to normal, and drainage from the sinuses gradually subsided. A few weeks after discharge the chest sinuses and the fistulous communication with the small bowel and vagina closed.

**Case 2**—A white woman, aged 44, was admitted to the hospital in August 1944 with an area of inflammation and draining sinuses on the right lateral chest wall of three months duration. Twelve months previously a supracervical hysterectomy with bilateral salpingo-oophorectomy was performed for chronic pelvic inflammatory disease, tubo-ovarian abscess, and fibromyoma of the uterus. The infected area was incised, drained, and curretted. Microscopic examination of pus showed actinomyces and sulfur granules.

A total of 500,000 units of penicillin was given intramuscularly by injection of 15,000 units every three hours. The sinuses were irrigated with a 5 per cent solution of penicillin four times daily. The inflammatory process subsided, and the amount of drainage noticeably decreased. After discharge, treatment continued by the referring physician brought the total course of penicillin to 2,000,000 units. Follow-up one month later showed a very satisfactory result with cessation of drainage and gradual closing of sinuses.

## SUMMARY

In two cases of actinomycosis treated with penicillin the infection developed after pelvic operations. The diagnosis in each case was proved by the presence of sulfur granules in the pus and by microscopic identification of actinomyces. Both patients had sinuses of the chest wall, and one had additional abdominal sinuses. Neither patient showed improvement prior to penicillin therapy. In one case 2,000,000 units and in the other 4,000,000 units of penicillin was given intramuscularly and by irrigation of sinuses. Pronounced improvement was noted in each case.

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# HYPERINSULINISM AND FUNCTIONAL HYPOGLYCEMIA

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The purpose of this article is to present two typical cases of hyperinsulinism associated with islet cell adenoma of the pancreas, to present four unusual cases of functional hypoglycemia, and to emphasize the differential diagnosis of these two conditions.

In this article the term "hyperinsulinism" is restricted to hypoglycemia due to adenoma of the islands of Langerhans, and the term "functional hypoglycemia" to hypoglycemia without clinical evidence of organic disorders commonly associated with hypoglycemia. Cases of obvious adrenal, pituitary, or liver disease are excluded. It is beyond the scope of this communication to review the etiology of hypoglycemia or cases reported in the literature.[1], [2], [3], [4]

## CASE REPORTS

**Case 1**—*Adenoma of pancreas cured by excision.* A man, aged 22, was seen on March 29, 1943 because of attacks characterized by trembling, weakness, sweating, and at times unconsciousness. The attacks began two and one-half years previously, occurred three or four times weekly, and were increasing in frequency and severity. They usually

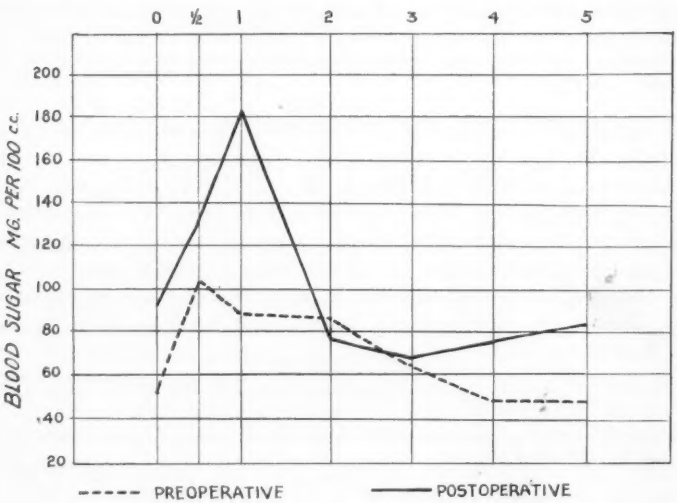


FIG. 1—Preoperative and postoperative glucose tolerance curves (case 1).

appeared at night but were often induced by exertion or fasting. The patient was repeatedly relieved by drinking orange juice. His illness was accompanied by a gain of 40 pounds.

Fasting blood sugar levels were 39 and 51 mg. per 100 cc. A single dose, hundred gram, oral glucose tolerance test on March 31 produced a curve as shown in figure 1. An insulin tolerance test on April 10 in which 5 units of standard insulin was given intravenously revealed the following:

| Minutes | Fasting | 20 | 30 | 40 |
|---|---|---|---|---|
| Blood sugar—mg. per 100 cc. | 52 | 33 | 33 | 40 |

Symptoms of stupor and drowsiness during the test were partly relieved by 7 minims of a 1:1000 solution of adrenalin.

The pancreas was explored on April 12 by Dr. T. E. Jones, and a benign adenoma 1 cm. in diameter was removed from the anterior surface of the body of the pancreas. The postoperative course was uneventful except for the development of a pancreatic fistula, which healed in two months.

The patient remained free from further attacks of hypoglycemia and lost 30 pounds. Glucose tolerance on June 30 became normal as shown in figure 1. The patient had been given a well balanced diet for one week prior to this test.

**Case 2**—*Adenoma of pancreas associated with menstrual disorder surgically cured.* A housewife, aged 30, first seen on January 24, 1944, complained of attacks of circumoral tingling, generalized nervousness, weakness, profuse drenching sweats, mental confusion,

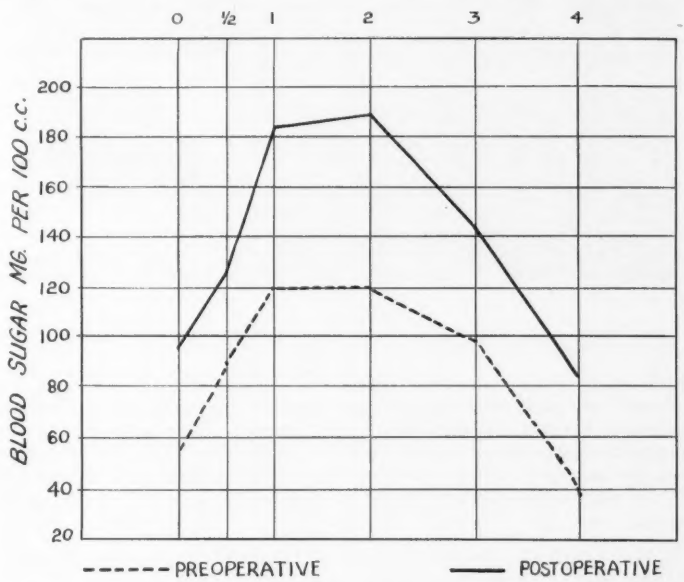


FIG. 2—Preoperative and postoperative glucose tolerance curves (case 2).

ptyalism, and unconsciousness. The attacks began four years previously and had increased in frequency and severity. They were precipitated by fasting and/or exercise and were relieved promptly by food. A weight gain of 30 pounds occurred. The menstrual cycle varied from twenty-eight to forty-two days. The flow was very dark on the first day and lasted from five to six days. Libido was absent.

At the time of symptoms blood sugar levels ranged repeatedly from 29 to 50 mg. per 100 cc. Random fasting blood sugar levels ranged from 37 to 46 mg. per 100 cc. but were not always accompanied by symptoms. A single dose, hundred gram, oral glucose tolerance test produced a curve as shown in figure 2. Adrenalin tolerance test after administration of 8 minims of 1:1000 adrenalin solution subcutaneously was as follows:

| Minutes | Fasting | 15 | 30 | 45 | 60 | 75 |
|---|---|---|---|---|---|---|
| Blood sugar—mg. per 100 cc. | 37 | 20 | 35 | 35 | 35 | 46 |

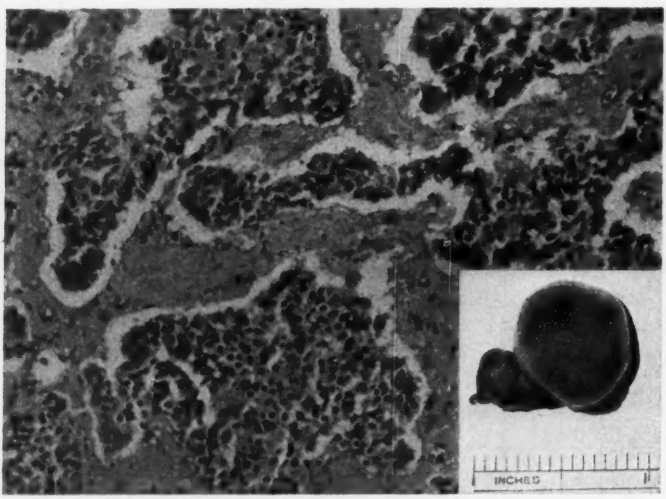


Fig. 3

On February 21 an exploratory laparotomy was performed by Dr. T. E. Jones. No adenoma was found. Since the patient's symptoms progressed during the next few months and were regarded as pathognomonic of islet cell hyperplasia, a second laparotomy was performed on June 4. An adenoma measuring 1.5 by 1.2 by 1 cm. was removed from the substance of the pancreas beneath the anterior surface of the first part of the tail (fig. 3). Microscopically this proved to be a benign adenoma of the islands of Langerhans.

The patient remained symptom free and by limiting food intake lost 11 pounds in three months without development of symptoms. On occasions she fasted fifteen hours without symptoms. The irregular menses previously described promptly became normal.

A glucose tolerance test two weeks postoperatively was normal (fig. 2). The diet preceding this test was regular and well balanced. An insulin tolerance test on June 19 failed to show any residual insulin sensitivity, and the response to 8 minims of adrenalin was altered slightly as follows:

| Minutes | 15 | 30 | 45 | 60 |
|---|---|---|---|---|
| Blood sugar—mg. per 100 cc. | 65 | 79 | 79 | 79 |

**Case 3**—*Functional hypoglycemia associated with sterility.* A woman, aged 32, complained of headaches, childlessness, and indigestion. She had been married for five years and had attempted pregnancy for three years. Menstrual periods were regular and normal. The headaches, which were frequent and lasted one to one and one-half hour, were experienced for five years, were usually unilateral, and often occurred during sleep or upon rising. Gaining weight or maintaining normal weight was difficult. Symptoms of indigestion were vague and consisted mainly of gas and belching.

Physical examination was essentially normal. An intradermal histamine test did not reproduce a typical headache. A single dose, hundred gram, oral glucose tolerance test revealed a curve in detail as follows:

| Minutes | Fasting | 30 | 60 | 120 | 180 | 240 |
|---|---|---|---|---|---|---|
| Blood sugar—mg. per 100 cc. | 82 | 107 | 75 | 45 | 60 | 79 |

A typical headache appeared at the second hour of the test.

The patient was placed upon a low carbohydrate, high protein, high fat diet. Both the headaches and the digestive distress were completely relieved. In the next three months she gained 16 pounds. The patient became pregnant approximately one month after she began the diet. Pregnancy and labor were normal.

One year later she was still symptom free but noted a recurrence of headaches with temporary dietary indiscretions. Two and one-half hours after eating the blood sugar level was 108 mg. per 100 cc.

**Case 4**—*Functional hypoglycemia associated with menstrual disorder.* A woman, aged 29, complained of irregular menses and nervousness. Menarche was at the age of 15. The periods were irregular from the start, occurring at intervals of twenty-three to thirty-three days, and lasted for five to seven days. She married at the age of 18 and promptly became pregnant. After delivery menstrual periods varied from twenty-one to thirty-eight or forty days. At times the flow lasted for ten days; spotting was common. Drainage of bilateral ovarian cysts elsewhere did not modify the menses. Intervals between periods became longer, and spotting continued. An endometrial biopsy on the twenty-sixth day of the menstrual cycle revealed an endometrial development consistent with that of the seventh or eighth day of a normal menstrual cycle.

The patient also complained of headaches, temporary confusion, weakness, excessive sweating, and severe hunger; these symptoms were frequently relieved by eating. She ate a great amount of rich food. Because of these symptoms suggesting hypoglycemia a single dose, hundred gram, oral glucose tolerance test was done and revealed the following:

| Minutes | Fasting | 30 | 60 | 120 | 180 | 240 |
|---|---|---|---|---|---|---|
| Blood sugar—mg. per 100 cc. | 91 | 96 | 92 | 35 | 95 | 37 |

Typical symptoms were experienced at the second and fourth hours of the test.

A low carbohydrate, high protein, high fat diet was prescribed. When the patient was seen about seven months later, the hypoglycemic symptoms were controlled. The last three menstrual periods occurred at twenty-eight to thirty-one day intervals. The flow was still prolonged but was more nearly normal in amount with less tendency to spotting between menses. Another endometrial biopsy on the twenty-sixth day of the menstrual cycle showed an endometrial development comparable with that of the twentieth to the twenty-second day of a normal cycle with evidence of secretory changes.

**Case 5**—*Functional hypoglycemia associated with unusual nail changes.* A housewife, aged 29, complained of redness, pain, and swelling of the nail beds with eventual deformity and loss of the nails. Other symptoms were anorexia, nausea and vomiting, excessive falling of scalp hair, cessation of menses, nervousness, and weakness. The fingernails of all but the fifth finger of the right hand and the fourth finger of the left hand were ridged. Along the edges the nails were rough and friable. At the base of the involved nails, except that of the second finger of the right hand, were paronychial changes with redness and swelling. Smears and cultures for fungus infection were negative. During diagnostic studies a glucose tolerance test was done and revealed the following:

| Minutes | Fasting | 30 | 60 | 120 | 180 | 240 |
|---|---|---|---|---|---|---|
| Blood sugar—mg. per 100 cc. | 81 | 107 | 88 | 53 | 63 | 63 |

The patient was placed on a low carbohydrate, high protein, high fat diet. Within two months all symptoms were alleviated. The fingernails were growing normally, although several remained deformed. She gained 10 pounds. After seven and one-half months her appetite was normal, and she had no attacks of weakness or nausea. Hair loss continued as did amenorrhea. Her fingernails were almost completely normal, being the best in four or five years.

**Case 6**—*Functional hypoglycemia associated with unusual nail changes.* A housewife, aged 39, complained of nervousness, palpitation, and tension in the neck muscles. General physical examination revealed no remarkable findings. A basal metabolic rate determination was normal. Vaginal smear tests ndicated normal ovarian function. Because symptoms were not adequately explained and since hypoglycemia was suggested, a glucose tolerance test was performed.

| Minutes | Fasting | 30 | 60 | 120 | 180 | 240 |
|---|---|---|---|---|---|---|
| Blood Sugar—mg. per 100 cc. | 108 | 150 | 94 | 74 | 93 | 34 |

Symptoms appeared at the fourth hour of the test.

All symptoms were relieved for seven months by dietary manipulation. She then disclosed that her fingernails had been affected by the illness. A separation of the nail beds of all fingers occurred repeatedly in the previous three years, four or five nails being simultaneously affected. The changes began as a sma l red spot usually in one corner or in the center of the nail. This area would spread to the periphery of the nail, and after a time the reddened area would turn white and separate from the nail bed (fig. 4). Several toenails were similarly involved. Fungus infection had been previously excluded. During the next eight months all of the nails became completely normal and remained normal as long as the patient observed the diet; nail changes recurred with dietary indiscretion.

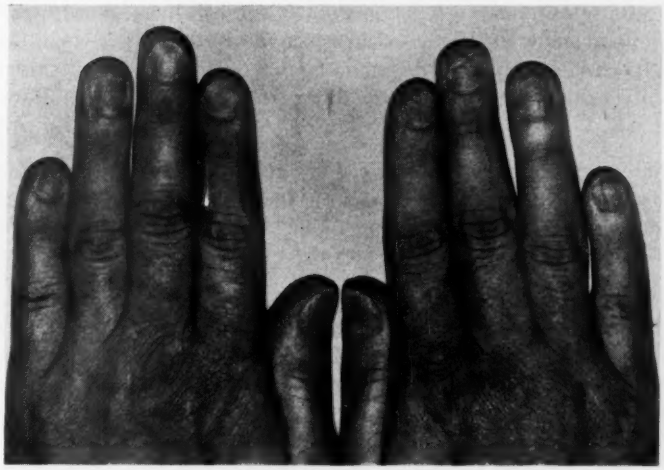

FIG. 4

## COMMENT

Certain important features serve to differentiate functional hypoglycemia and hyperinsulinism. In hyperinsulinism the hypoglycemic episodes are usually more profound and tend to increase in frequency and severity. Attacks are often induced by fasting and/or vigorous muscular activity. The patient frequently discovers that food promptly relieves the symptoms, and consequently the total daily caloric intake is usually increased. Weight gain is thus a common accompaniment, unless the pancreatic lesion is malignant. Dietary manipulation usually fails to alleviate symptoms. Of these features the most important is intolerance to fasting and exercise. The diagnosis is strengthened by a fasting blood sugar level consistently below 60 mg. per 100 cc. More often the fasting blood sugar level is 50 mg. per 100 cc. or lower. Such a patient may be found unconscious during the night or before breakfast.

In contradistinction functional hypoglycemia is more bizarre in its clinical manifestations and thus more difficult to recognize. The symptoms are usually less severe and do not tend to progress. The patient is less apt to discover that symptoms are relieved by food, since hunger is not an outstanding symptom. Thus weight gain is not common; in contrast malnutrition is frequently observed. Dietary manipulation almost invariably controls and often corrects hypoglycemic trends and usually completely rehabilitates the patient. Fasting and exercise may

accentuate symptoms but less consistently than in hyperinsulinism. The fasting blood sugar may be low but is usually well within normal range. Hypoglycemia is most often apparent two to four hours after eating, especially with excessive carbohydrate intake after several hours of fasting.

These contrasting features are demonstrated by the cases reported. The functional cases are chosen mainly because of unusual features that have been corrected by treatment in such a way as to suggest strongly that they were intimately related to the hypoglycemia.

In case 3 we believed that the headaches were of hypoglycemic origin. Whether or not the apparent infertility was directly related to hypoglycemia, to malnutrition, or to totally unrelated causes is speculative. However, it is interesting that pregnancy occurred promptly after the diet was begun and before malnutrition was corrected or further studies of sterility were obtained. A further correlation is suggested between ovarian function and hypoglycemia in cases 2 and 4, because irregular and scant menses approached normal after the adenoma was removed.

In cases 5 and 6 unusual nail changes accompanied the hypoglycemia. In one instance the nails became completely normal, and in the other they remained healed as long as the patient adhered to the diet.

## SUMMARY

Certain criteria are important in the differential diagnosis of hyperinsulinism with adenoma of the pancreas and functional hypoglycemia. Two typical cases of hyperinsulinism due to islet cell adenoma of the pancreas were encountered, both of which remained well after excision of the tumor. In four cases of functional hypoglycemia sterility occurred in one, a menstrual disorder in one, and nail changes in two.

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